Post-transplant care after allogeneic hematopoietic stem cell transplantation

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Received: 12.01.2015. Accepted: 24.02.2015.

ABSTRACT

Around 25,000 people annually worldwide are subject to the procedure of allogeneic hematopoietic stem cell transplantation (HSCT). As the number of procedures has been on the rise, post-transplant care is becoming an essential part of work at transplant centres and general practitioners' offices. Advances in technology and supportive therapies extend long-term survival of patients after HSCT, which increases the risk of complications resulting from exposure before, during and after transplant procedures. The complications may lead to significant morbidity, deteriorated quality of life, and late mortality in patients who have received hematopoietic stem cells. Statistical analyses have shown that the survival rate of post-HSCT patients is ca. 30% lower than expected, and that infections, organ failure and secondary cancers lead to mortality in this population of patients.

KEY WORDS: hematopoietic stem cell transplantation, post-transplant care, post-transplant complications

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Each year around 25,000 people globally undergo an allogeneic hematopoietic stem cell transplantation (HSCT). With the number of transplantation procedures growing steadily, post-transplant care is becoming an essential part of work at transplant centres and general practitioners' offices. Advancements in technology and supportive therapies extend long-term survival of patients after hematopoietic stem cell transplantation which increases the risk of complications resulting from exposure before, during and after transplant procedures. The complications may lead to significant morbidity, deteriorated quality of life and late mortality in patients who have received hematopoietic stem cells. Statistical analyses have shown that the survival rate of post-HSCT patients is ca. 30% lower than expected, and that infections, organ failure and secondary cancers lead to mortality in this patient group [1, 2, 5, 21].

TASKS OF OUTPATIENT TRANSPLANT CLINICS

1. **Remission control**

   The key responsibility of an outpatient transplant clinic is controlling the remission of the primary condition. At the initial consultation, the clinic should estimate the individual risk of recurrence on the basis of the patient's response to prior treatment, assess the extent and severity of the minimal residual disease and identify the specific tumour markers (phenotypic, cytogenetic and molecular markers) which will be used in scheduled tests of bone marrow and peripheral blood [1–3]. Following an allogeneic hematopoietic stem cell transplantation, the patient becomes a chimera because he/she has genetically distinct cells from the donor in his/her bone marrow and peripheral blood. The proportion of donor and recipient cells is assessed on the basis of chimerism tests. Results of chimerism testing help to determine the effectiveness of allo-HSCT and establish the extent to which the recipient's hematopoietic system is built from the donor's cells. The tests are particularly relevant for patients who have undergone a reduced-intensity conditioning regimen (RIC) where the recipient's cells are not destroyed entirely. Regular testing of chimerism over time contributes to early detection of recurrence of the primary condition. Chimerism tests, when used to monitor the changing percentage of recipient and donor cells, are crucial for managing the immunosuppressive treatment and assessing the risk of graft-versus-host disease (GvHD) [1–3]. A range of different cell populations in the blood and bone marrow may be used for chimerism testing. From the prognostic perspective, the most valuable counts are those performed on cell lines from which the cancerous cells originate. It is also highly beneficial to test chimerism in the T-lymphocyte subpopulation due to its role in the graft-versus-leukaemia/cancer (GvL) effect. A chimerism test with the longest history is the blood type test which is conducted when the recipient and donor have different erythrocyte antigens. This test, however, does not yield a precise result due to peri-operative transfusions and a long lifespan of erythrocytes. When analysing chimerism in sex-mismatched donor/recipient pairs, a fluorescence in situ hybridization (FISH) method can be applied using sex chromosome-specific probes. In case of histoincompatibility between the donor and the recipient, a human leukocyte antigen (HLA) test can be performed. At present, the most commonly used chimerism tests include highly sensitive and informative molecular techniques such as the detection of donor- and recipient-specific microsatellite markers using the short tandem repeats-polymerase chain reaction (STR--PCR) method, and the real-time polymerase chain reaction (RT-PCR) method exploring the biallelic polymorphism found in the genome.

The most desirable outcome is a complete chimerism (CC) which is established when only the donor's characteristics and DNA are present in the sample (> 95%). This status is associated with a complete remission and a progression-free survival [3]. When both the donor's and the recipient's DNA is detected in the sample, a mixed chimerism is identified which can be stable or transient. A stable mixed chimerism (SMC) is recognised when the donor/recipient cell proportion remains steady long after HSCT and a transient mixed chimerism (TMC) is identified when the proportion of the donor's characteristics and DNA grows in subsequent tests (by 5%) until a CC is achieved. A SMC occurs at an early stage after a transplantation with a reduced-intensity conditioning (RIC) regimen. However, when a SMC persists for a longer period, it may indicate that an immunological tolerance was established between the donor and the recipient cells and is a sign of an increased risk of recurrence (due to a weaker GvL effect). In case of a mixed chimerism, it is recommended to test chimerism once a week or 2 weeks until day 100, and afterwards once a month up to 18 months until a complete chimerism is confirmed by two consecutive tests. When the percentage share of the recipient's DNA increases by 5% in consecutive tests, then a progressive mixed chimerism (PMC) is identified which may be regarded as evidence of recurrence at the molecular level, and indicates that immunomodulative treatment should be initiated (immunosuppressive treatment need to be discontinued

and donor lymphocyte infusions should be considered). Allo-HSCT are increasingly often performed on patients at a high risk of recurrence, therefore it has become very important in recent years to plan a post-transplant consolidation therapy to sustain the remission effect (e.g. by use of demethylating agents in myelodysplasia and tyrosine-kinase inhibitors in case of BCR/ABL rearrangements etc.) and to competently use donor lymphocyte infusions for treatment of the residual disease.

2. Preventing the graft-versus-host disease

The graft-versus-host disease is one of the most serious and potentially fatal complications related to HSCT. It affects 30–50% patients receiving cells from family donors and approx. 60% patients receiving cells from unrelated donors. GvHD may develop despite intensive immunosuppressive therapy. The disease occurs when three conditions are met: immunocompetent cells are transferred to the recipient, the donor and the recipient are histoincompatible and the recipient is unable to inactivate the transplanted cells [1, 2]. According to the definition of the U.S. National Institutes of Health's (NIH) Consensus Conference, the GvHD can be acute or chronic. Both forms have several subcategories. In order to distinguish between the acute and chronic form, one should be guided by the clinical monitoring of the disease and a set of characteristic symptoms (rather than the time criterion [day 100] prescribed in the Seattle classification) [1–3]. Both forms of the GvHD have different pathomechanisms. The acute form is primarily inflammatory. The key mechanism in an acute GvHD is the mutual interaction between the activated recipient's antigen-presenting cells and the donor's lymphocytes, as a result of which proinflammatory cytokines are secreted. This leads to apoptosis of the tissue layer which regulates proliferation and regeneration, namely the basal layer of the epidermis, epithelium in the alimentary tract and cells of the epithelium lining the bile ducts [6, 7]. An acute graft-versus-host disease may manifest itself in a classic acute form which occurs within 100 days after a hematopoietic stem cell transplantation or a donor lymphocyte infusion (DLI). An acute classic form of GvHD presents with skin symptoms such as erythematous papular rash and formation of blisters, gastrointestinal symptoms such as diarrhoea, mostly green and watery, nausea and vomiting, as well as cholestatic hepatitis frequently co-occurring with jaundice. Other forms of an acute graft-versus-host disease include persistent, recurrent and late-onset GvHD which occur more than 100 days after the transplantation [1, 3].

A chronic GvHD is an immunological process, affecting multiple organs and resembling other autoaggressive diseases such systemic sclerosis, Sjögren's syndrome, primary biliary cirrhosis, obliterative bronchiolitis and immune cytopenia. The key role in the pathomechanism of a chronic GvHD is played by chemo/radiotherapy-induced damage to the thymus, disrupted negative selection of alloreactive T-lymphocytes, formation of autoreactive B-lymphocytes and macrophage activation leading to fibroblast proliferation [6, 7]. According to the definition of the NIH, the symptoms of a chronic graft versus host disease (cGvHD) may be pathognomonic (which are sufficient to diagnose the disease) and distinctive (which require a confirmation by means of a histopathological exam or a different laboratory test). A chronic GvHD manifests as a classic form or a mixed form also called an overlap syndrome in which symptoms of a chronic disease are concomitant with symptoms of an acute disease. The following organs need to be examined: skin, oral mucosa, eyes, alimentary canal, liver, lungs, muscles, fascia, joints, genitals and the hematopoietic system. In addition, the patient should be examined for presence of such complications as oesophageal stricture, exudative pleuritis and pericarditis, ascites, nephrotic syndrome, myasthenia gravis, polymyositis, cardiomyopathy, peripheral neuropathy, thrombocytopenia, eosinophilia and other. The severity of a cGvHD is determined based on the number of involved organs and the extent of damage to the affected organs (where '0' means an organ is not affected at all and '3' represents a severe damage to an organ) [1, 6, 7].

Doctors taking care of post-HSCT patients face a difficult task of having to competently manage immunosuppressive therapy, as well as accurately diagnose and effectively manage a GvHD. Emphasis must be placed on an individual case-by-case approach to therapy and selection of the most appropriate prophylactic treatment for the patient. For each patient, the risk factors of GvHD development must be assessed. These include the degree of HLA mismatch, the relatedness between the donor and the recipient, the source of hematopoietic cells and other. On the other hand, the risk of disease recurrence must also be estimated. These factors need to be taken into account when choosing the type and timing of immunosuppressive therapy. Over the last few years, efforts have been made to find specific laboratory biomarkers to help identify patients at a high risk of a GvHD. Preventive immunosuppressive therapy must be selected depending on the type of hematopoietic cells transplantation used. The following factors need to be considered: the

conditioning regimen (myeloablative or reduced intensity) and the type of donor (matched family or unrelated donor). At the same time, results from chimerism tests must be checked.

Immunosuppressive therapy should must be monitored on a regular basis to ensure its efficacy and lowest possible toxicity. As the patient also simultaneously takes a wide range of other medications, including for instance prophylactic anti-infective agents, potential drug interactions must be taken into account. A patient receiving an immunosuppressive therapy is required to be closely monitored. For this reason, post-transplant care must be organised in such a way as to ensure the doctor can see the patient regularly, even once or twice a week in the period immediately following the transplant. Agents which are used to prevent a GvHD include calcineurin inhibitors (cyclosporine A, tacrolimus), methotrexate, anti-thymocyte globulin (ATG), mycophenolate mofetil and mTOR inhibitors (sirolimus). Table 1 shows the doses and recommended therapeutic concentrations of the above mentioned drugs in relation to the time elapsed from the hematopoietic cell transplant and the type of procedure performed. The data is based on the Bone Marrow Transplantation guidelines. According to a guiding principle, the patient should receive an intensive immunosuppressive therapy early after the transplant. Over time, the strength of therapy is gradually reduced. In order to reach the recommended concentrations of the agents, the doses need to be modified by 10–15%. Early after the transplant, patients who have undergone a reduced-intensity conditioning regimen are recommended to receive a more intensive immunosuppressive therapy (with higher concentrations of immunosuppressive agents) relative to patients who have received the myeloablative regimen. It is not advisable to discontinue a number of different immunosuppressive agents at the same time.

The most frequent adverse effects of calcineurin inhibitors include hypertension, electrolyte disorders (hypomagnesemia, hyperkalaemia), neurological symptoms (tremors, ataxia), hirsutism, renal failure, liver damage and thrombotic microangiopathy. The doses of calcineurin inhibitors must be modified depending on the level of creatinine. The use of mycophenolate mofetil is associated with a risk of cardiovascular complications (hypertension, oedemas) and gastrointestinal symptoms (diarrhoea, nausea).

In patients who have undergone myeloablative conditioning, glucocorticoids may be used for the prevention of a GvHD. To this end, patients are initially given methylprednisolone (0.25–0.5 mg/kg/day) intravenously, and later oral prednisone. The dose of glucocorticoids should be reduced by 5–10% per week from day (+30) to 10 mg of prednisone. This dose should be maintained until the dosage of calcineurin inhibitors is tapered.

3. Assessment of immune reconstitution

A hematopoietic cell transplantation compromises the immune system. Reconstitution of the immune system is a multistage process and a full immune recovery often takes several years. After the conditioning procedure, an aplasia phase occurs in which all elements of the immune system are destroyed. Depending on the type of the transplantation procedure and the source of progenitors, aplasia takes from 14 days (in case of a peripheral blood stem cell transplantation) up to 30 days (in case of a transplantation of hematopoietic stem cells from the core blood). In the aplasia phase, disorders of phagocytic function prevail which occur as a result of an impairment to non-specific immune mechanisms (e.g. agranulocytosis and the absence of other mononuclear phagocytes including monocytes and macrophages). This creates favourable conditions for the development of severe bacterial infections (including mostly endogenous infections caused by opportunistic bacteria) and fungal infections. After this phase is complete, a gradual recovery occurs and a granulopoiesis begins (albeit inefficient at first). Next, the first cytotoxic cells and the first population of regenerative lymphocytes called the natural killer (NK) cells are generated [1–4, 10–15]. At that point, the patient usually leaves the transplantation ward and is referred to an outpatient transplant clinic. However, the immune reconstitution is not yet complete. In the first 100 days after the HSCT, the acquired humoral and cellular immunity is still significantly compromised, while the counts of B- and T-lymphocytes from all populations decrease or their function becomes impaired. In this period, patients recovering after HSCT are particularly susceptible to viral and fungal infections, including infections caused by *pneumocystis jiroveci*. Owing to thymus damage caused by the conditioning regimens (radio- and chemotherapy), T-lymphocytes are initially regenerated through a thymus-independent pathway rather than by repeating the ontogenesis process [10–15]. The recipient's mature T-lymphocytes which survived the conditioning process and the donor's T-cells in the transplanted

TABLE 1.
Prophylactic doses of oral immunosuppressive agents for patients after allo-HSCT [1].

Agent	Dose for oral administration	Recommended concentration	
		Myeloablative conditioning	Reduced-intensity conditioning
Cyclosporine	3–4mg/kg every 12 hrs	Days: 0–28 200–300 ng/ml	Days: 0–28 300–400 ng/ml
		Days: 29–100 100–200 ng/ml	Days: 29–56 250–350 ng/ml
Tacrolimus	0.025–0.03 mg every 12 hrs	5–10 ng/ml	5–15 ng/ml
Rules for tapering dosage of calcineurin inhibitors		5–10% of dose per week from day (+100) until day (+180)*	6% of dose per week from day (+56) until day (+180)**
Sirolimus 12 mg on the first day, and 4 mg per day thereafter		3–12 ng/ml concentration Reduction of the dose by one-third every 9 weeks from day 60–90	
MMF (mycophenolate mofetil) 15 mg/kg			MRD-HCT – 2 doses per day from day +28 MUD-HCT – 3 doses per day on days 0–28, subsequent reduction to 2 doses per day and gradual discontinuation by day +56

* longer, until day (+360) in case of aplastic anaemia
** longer when mixed chimerism persists
MRD – HLA-matched related donor
MUD – HLA-matched unrelated donor.

material become activated (through contact with the antigen and under the influence of cytokines) and start differentiating again into effector cells and memory cells. This pathway of T-lymphocytes regeneration plays a key role and benefits the immune recovery but has its quantitative and qualitative limitations. Lymphocytes developing through this pathway have quality defects resulting from limited TCR diversity, which leads to an increased risk of infection regardless of the correct T-cell count. The thymus-independent pathway of T-cells regeneration is much more effective for CD8 cells than CD4 cells. There is a delay in CD4+ lymphocytes regeneration as a result of which the CD4/CD8 ratio is reversed and remains so for up to 12 months. Another reason why the cellular immunity which develops after the transplant is insufficient is the loss of immunological memory. This not only leads to frequent infections but also renders patients unable to respond to vaccines against a set of classic antigens. Only at six months after the transplant, the thymus is ready to take responsibility for the regeneration process, bringing the T-lymphocyte count to normal levels and restoring their functions. Thanks to the rearrangement of genes encoding the T-cell receptor which takes place in the thymus, the virgin lymphocytes are capable of responding to a whole range of pathogens to which the host is exposed. Age is the key factor determining the role played by thymus in T-cell regeneration. In adult patients, thymic involution significantly impairs reconstitution. The developing GvHD impairs the thymic function [2, 3].

B-cells are reconstituted earlier than T-cells, and their recovery mirrors the ontogenesis process. However, their count is significantly reduced for at least the first 3 months after the transplantation (in case of memory B-cells, for up to 2 years!). Early after the transplant, the recipient's radio- and chemotherapy-resistant plasma cells which survived the conditioning process may produce significant amounts of IgG antibodies. Over time, their amount decreases which is shown by the dropping levels of antibodies. After approx. 4 to 6 months, virgin B-cells are produced from the donor's progenitor cells which generate IgM antibodies. IgG (IgG1 and IgG3 subtype) are generated after 12–18 months while IgA, IgG2 and IgG4 – after 6–36 months. Assessment of IgG level alone is not a representative measure for B-cell reconstitution because the generated immunoglobulins have a reduced diversity and oligoclonality. The only measure which serves to determine whether humoral immunity is sufficient is the growing level of antibodies after a vaccination or an infection. A delayed production of IgG2 and IgG4, particularly in patients with a GvHD, may compromise the T-cell-independent response to polysaccharide antigens. At least for one year after the transplantation, the patients remain

susceptible to infections induced by encapsulated bacteria and viruses against which neutralising antibodies are the first line of defence. Therefore, vaccinations need to be provided and antiviral prophylaxis has to be maintained at least for one full year after the HSCT. Complex quantitative and qualitative deficiencies in immune cells lead to multimicrobial infections, typical for this group of patients [1–4].

Patients suffering from a GvHD represent a particular group among post-transplant patients. This patient group experiences the most severe and long-lasting difficulties with immune reconstitution which are further exacerbated by the immunosuppressive therapy provided for prophylaxis. Therefore, these patients are recommended to receive prophylaxis against infections until their immunosuppressive therapy is completed. Assessing immune reconstitution is a crucial task for doctors at outpatient transplant clinics. As part of routine diagnostic tests performed on post-HSCT patients, it is worthwhile to regularly check the level of CD3+4+ T-lymphocytes which, according to clinical studies, may be regarded as a prognostic factor. A drop in CD3+4+ T-lymphocytes below 200/μl is associated with a shorter overall survival (OS) and a higher non-relapse mortality (NRM). The level of CD3+4+ cells and the CD4/CD8 ratio are an important measure showing whether reconstitution is effective. It also helps to assess the risk of infection development and is useful for determining the timing of decontamination [2, 3]. According to EBMT guidelines, prophylaxis against *pneumocystis jiroveci* and VZV/HSV should be mandatory until the patient's level of lymphocytes CD4 rises above 200–400/μl. Subpopulation lymphocyte counts also help to make the decision when to start vaccinations. A CD4 lymphocyte level above 200/μl is considered sufficient to guarantee effectiveness of vaccinations.

4. Preventing infections in accordance with NIH 2012 guidelines [2, 5, 16–20]

A. PREVENTING BACTERIAL INFECTIONS

Patients who have undergone HCT and suffer from neutropenia for over 7 days after the transplantation need to receive prophylaxis against infections caused by Gram-negative bacteria in the period from day 0 to day 100. The therapy is based on fluoroquinolones such as levofloxacin (1 × 500 mg) or ciprofloxacin (2 × 500 mg) – selection between these agents must always be made after a careful assessment of epidemiological data due to growing immunity of bacterial strains – or azithromycin (1 × 250 mg).

Patients need to receive preventive therapy against infections caused by *streptococcus pneumoniae* until vaccinations are completed or for a longer period in case of a chronic active GvHD which requires immunosuppressive therapy and in case of hypogammaglobulinemia. Prophylaxis is based on phenoxymethylpenicillin (2–3 × 1000–1500 IU p.o.). In case of intolerance, macrolides, quinolones or cephalosporins may be used. When the patient needs a dental procedure, measures must be taken in order to prevent infective endocarditis in accordance with AHA 2007 guidelines. Patients suffering from recurring infections and a severe hypogammaglobulinemia (IgG < 400 mg%) may be considered for an immunoglobulin substitution therapy at a dose of 0.5 g/kg every 3–4 weeks. However, immunoglobulin substitution is not recommended to be routinely used for prophylaxis.

B. PREVENTING FUNGAL INFECTIONS

Antifungal prophylaxis needs to be continued until immunosuppressive therapy is completed.

A standard antifungal therapy is based on:

- fluconazole (200–400 mg p.o.), posaconazole (3 × 200 mg p.o.) – these agents are available for outpatient treatment in Poland
- itraconazole (2 × 200 mg; an oral solution is unavailable in Poland), micafungin (1 × 50 mg i.v.), voriconazole (2 × 200 mg p.o.).

Patients who are at a high risk of infections caused by moulds or fluconazole-resistant *Candida* species are recommended to receive prophylaxis based on:

- micafungin (1 × 50 mg) – in case of a protracted neutropenia
- posaconazole (3 × 200 mg) or voriconazole (2 × 200 mg p.o.) – in case of a GvHD.

Patients are also recommended to receive prophylaxis against *pneumocystis jiroveci* (and *toxoplasma gondii* in case of seropositive recipients) for at least 6 months after HSCT or until the immunosuppressive therapy is completed. The prophylaxis is based on trimethoprim/sulfamethoxazole (TMP-SMX) 2 × daily at 960 mg twice a week (allergic patients need to undergo desensitization regimens).

C. PREVENTING VIRAL INFECTIONS

Prophylaxis against VZV and HSV is recommended to be provided during the first year after allogeneic HSCT or for a longer period in case of patients suffering from a GvHD and receiving an immunosuppressive therapy. The therapy is based on aciclovir (2 × 800 mg p.o.) taken every 12 hours. In the flu season, oseltamivir (75 mg/day) is recommended as prophylaxis against influenza A and B virus (in the first 24 months after HSCT regardless of vaccinations and for all patients suffering from a GvHD and receiving an immunosuppressive therapy). Tests recommended to identify a CMV infection include molecular tests which detect viral DNA or mRNA as well as pp65 antigen tests performed on peripheral blood leukocytes using a immunoenzymatic method. CMV-seropositive recipients and recipients of cells from CMV-seropositive donors are at a risk of a CMV reactivation. In addition to ganciclovir and foscarnet, an oral formulation of acyclovir at a dose of 4 × 800 mg is also allowed for primary prophylaxis against CMV infections. In addition to that, patients must be regularly monitored to establish a possible reactivation of a previous CMV infection. For CMV-seropositive recipients, the risk of CMV reactivation is above 50% (45–86%) while the risk of CMV disease development is 20–30%. Anticipative therapy is superior to prophylactic therapy only for seronegative recipients who received cells from seropositive donors. In all other cases, a CMV anticipative therapy may only be considered after obtaining two subsequent positive tests. A therapy based on oral valganciclovir may be initiated when the patient is not feverish, there is no evidence of organ damage (pneumonia, renal failure etc.) and the number of virus copies is below 5000/ml. It is recommended to prescribe valganciclovir in the dose of 2 × 900 to be taken for 7–14 days, and later in the dose of 1 × 900 until two subsequent negative tests are obtained. In all other cases, the patient needs to be admitted to hospital and receive parenteral ganciclovir first at a dose of 2 × 5 mg/kg/day for 7–14 days, and later at a dose of 1 × 5 mg/kg/day or foscarnet at a dose of 2 × 60 mg/kg i.v. as well as intravenous immunoglobulin. It should be stressed that the number of late CMV reactivations has grown recently.

5. Providing vaccinations

Patients who have undergone an allogeneic hematopoietic stem cell transplantation need to receive inactivated vaccines. It is not advisable to delay vaccinations for patients suffering from a GvHD. Live vaccines (e.g. vaccines with measles, mumps and rubella viruses) may be considered after 24 months from the transplant in case of adult seronegative patients but must **not** be used in case of patients with an active GvHD **and** patients during an immunosuppressive treatment [2, 4, 8, 9]. The vaccination plan includes vaccines against the following microorganisms:

1. *Streptococcus pneumoniae*
   - A 13-valent pneumococcal conjugate vaccine (PCV--13) is used at 3 to 6 months after the HSCT. It is recommended to administer three doses of PCV-13 at one-month intervals, to be followed by a fourth dose of 23-valent polysaccharide pneumococcal vaccine (PPSV23) for a broader protection (in case of patients suffering from a cGvHD who frequently fail to respond to the vaccine, a fourth dose of PCV--13 may be considered).
2. *Haemophilus influenzae* B
   - It is recommended to immunise the patient with 3 doses of conjugate vaccine at one-month intervals at 6 to 12 months after the transplantation.
3. *Neisseria meningitidis*
   - Patients need to receive one dose of a conjugate vaccine at 6 to 12 months after the transplantation.
4. *Tetanus, diphtheria, acellular pertussis* and polio
   - Patients are recommended to receive vaccines containing a full dose (30 units) of diphtheria toxoid in combination with a tetanus toxoid (40 units) and a full dose of acellular pertussis toxoid (0.04 mg) as well as an inactivated poliovirus (DTaP-IPV vaccines). According to recommendations, patients should receive three vaccines at one-month intervals at 6 to 12 months after the HSCT.
5. Influenza A and B virus
   - Patients need to be immunised each year. The first vaccination should take place at 4 to 6 months after the HSCT (patients need to receive available vaccines with strains AH3N2 + AH1N1+ B).
6. Hepatitis B virus
   - Vaccination is recommended to take place at 6 to 12 months after the transplantation. Three doses of the vaccine need to be administered. The effectiveness of immunisation is assessed on the basis of a test for anti-HBs antibodies. Patients who have not become immune despite being vaccinated (their result of the anti-HBs test is positive at > 10 IU/ml while immunity is achieved when the result is > 100 IU/ml) need to be re-vaccinated, and double doses are permitted.

TABLE 2.
Vaccination plan for patients post-allo-HSCT [2, 8, 9].

Vaccine	Time of administration after HSCT	No. of doses
Pneumococcal conjugate vaccine (PCV-13) Polysaccharide pneumococcal vaccine – PPSV23	3–6 months	3 1
Meningococcal conjugate vaccine	6–12	1
Conjugate *haemophilus influenzae* vaccine	6–12	3
Vaccine against *tetanus, diphtheria, acellular pertussis* and inactivated poliovirus	6–12	3
Hepatitis B vaccine	6–12	3
Influenza vaccine	4–6	1

A proposed vaccination plan is shown in Table 2.

Patients after allogeneic hematopoietic stem cell transplantations experience pathological symptoms in all organs. Therefore, collaboration with a multidisciplinary medical team is a vital part of operation of an outpatient transplant clinic. Non-infection induced complications affecting body organs result from previous treatment, including toxic conditioning regimens (chemo- and radiotherapy), prior infectious complications, the graft-versus-host disease and its treatment. The tasks of a doctor at an outpatient transplant clinic include treatment of the GvHD, and diagnosis and treatment of other non-infection induced complications affecting organs, including secondary tumours.

These topics will be discussed in a separate paper.

Acknowledgements

Authors report no conflict of interest.

References

1. The BMT Data Book, 2nd edition. Munkers R, Lazarus H, Atkinson K (ed.). Cambridge Medicine.
2. The EBMT Handbook, 6th edition, 2012. Apperley J, Carreras E, Gluckman E. (ed.).
3. Witt M, Szczepański T, Dawidowska M. Hematologia molekularna – patogeneza, patomechanizm i metody badawcze [Molecular haematology – pathogenesis, pathomechanism and research methods]. Ośrodek Wydawnictw Naukowych 2009.
4. Gołąb J, Jakóbisiak M, Lasek W et al. Immunologia [Immunology]. PWN, Warszawa 2008.
5. Guidelines BMT 2009; 44: 457-536.
6. Blazar B, Murphy W, Abedi M. Advances in graft-versus-host disease biology and therapy. Nature Reviews Immunology 2012; 12: 443-458.
7. Ferrar J, Levine J, Reddy P et al. Graft-versus-Host Disease. Lancet 2009; 2: 1550-1561.
8. Rubin L, Levin M, Ljungman P. 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised host. Clinical Infectious Diseases 2014; 58: e44-e100.
9. Medycyna Praktyczna Szczepienia 2014/01 [Practical Medicine Journal – Vaccinations, 2014/01 issue].
10. Fry T, Mackall C. Immune reconstitution following hematopoietic progenitor cell transplantation; challenges for the future. BMT 2005; 35: S53-57.
11. Maury S, Mary J, Rabian C et al. Prolonged immune deficiency following allogeneic stem cell transplantation: risk factors and complications in adult patients. British Journal of Haematology 2001; 115(3): 630-641.
12. Mackall C, Fry T, Gress F et al. Background to hematopoietic cell transplantation, including post transplant immune recovery. BMT 2009; 44: 457-462.
13. Storek J, Dawson M, Storer B. Immune reconstitution after allogeneic marrow transplantation compared with blood stem cell transplantation. Blood 2001; 97(11): 3380-3389.

14. Lum L. The kinetics of immune reconstitution after human marrow transplantation. Blood 1987; 69: 369-380.
15. Seggewiss R, Einsele H. Immune reconstitution after allogeneic transplantation and expanding options for immunomodulation: an update. Blood 2010; 115(19): 3861-3868.
16. Tomblyn M, Chiller T, Einsele H et al. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective. Biol Blood Marrow Transplant 2009; 15: 1143-1238.
17. Maertens J, Marchetti O, Herbrecht R et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3 – 2009 Update. Bone Marrow Transplantation 2011; 46: 709-718.
18. Zaia J, Baden L, Boeckh M. Viral disease prevention after hematopoietic cell transplantation. Bone Marrow Transplantation 2009; 44: 471-482.
19. Marr K, Bow E, Chiller T et al. Fungal infection prevention after hematopoietic cell transplantation. British Committee for Standards in Haematology; Guidelines on the management of invasive fungal infection during therapy for haematological malignancy, British Committee for Standards in Haematology. BMT 2009; 44: 483-487.
20. Gratwohl A, Brand R, Frassoni F et al. Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukemias: an EBMT analysis of lethal infectious complications and changes over calendar time. BMT 2005; 36: 757-769.
21. Jędrzejczak W. Aktualne wskazania do przeszczepienia komórek krwiotwórczych komórek macierzystych [Current indications for hematopoietic stem cell transplantation]. Acta Haematologica Polonica 2009; 40: 305-311.

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Jadwiga Dwilewicz-Trojaczek: 20%